TOXIC EFFECTS OF THERAPEUTIC AGENTS

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR PAUL REZNIKOFF: The subject of this Panel Meeting is "Toxic Effects of Therapeutic Agents." It is quite obvious that we cannot cover all of the toxic effects of all therapeutic agents and, therefore, in the limited time we have, and because we wish to allow some time for questions, our speakers will stress only some of the outstanding problems in this field.

I will introduce the members of the Panel: Dr. Harry M. Rose, John E. Borne Professor of Medical and Surgical Research at the College of Physicians and Surgeons, Columbia University and Executive Officer of the Department of Microbiology at that institution, as well as Attending Microbiologist at Presbyterian Hospital. He will talk to us on the subject of the general effects. Dr. Marvin Stern, Associate Professor of Clinical Psychiatry, at New York University College of Medicine and Associate Visiting Neuropsychiatrist at Bellevue Hospital, will discuss the neuropsychiatric aspects. Dr. Louis R. Wasserman is Director of the Department of Hematology of The Mount Sinai Hospital of New York, and he will tell us about the toxic effects of therapeutic agents on the hematopoietic system. So without any further delay I shall first call upon Dr. Rose.

DR. HARRY M. ROSE: This is an extremely broad topic, and it is impossible to cover it in the time allotted, even though Dr. Reznikoff has instructed me to forego any discussion of toxic effects which result in blood dyscrasias or psychiatric disorders.

What do we mean by toxicity? Certainly we do not refer to the narrow region defined by the strict meaning of the word, coming from the Latin *toxicum*, a poison, which is itself derived from *potio*, a dangerous draught of liquid with direct noxious effect. I think that toxicity would best be defined in this discussion as the undesirable effect of a therapeutic agent which differs from its expected action and is harmful to the patient. With this definition in mind, it is clearly possible to consider toxicity of therapeutic agents from two main points of view:

1. Toxic reactions which are related to their direct effects on physiological processes; and

2. Reactions caused by indirect effects of the agents, generally as the result of an abnormal response by the recipient.

As an example in the first category we may cite morphine, which is well known to cause toxic reactions if the proper dose is exceeded, and in the second category, penicillin, which can cause severe or even

fatal anaphylactic reactions in patients who have become hypersensitive to this antibiotic.

In general, leaving aside those reactions which involve the hematopoietic system or provoke psychiatric disturbances, toxicity is manifested by signs and symptoms referable to the nervous system, liver, kidneys, cutaneous tissues, and gastrointestinal tract, or by systemic phenomena of which fever is the outstanding example.

Since it is obviously impossible to discuss all therapeutic agents, I am going to confine my subsequent remarks to drugs which have been more recently introduced, and particularly to antibiotic or chemotherapeutic compounds.

First, with respect to the direct toxic action of these agents, a few examples may be noted. Sulfamethylthiazole, one of the earlier sulfonamide drugs, frequently caused peripheral neuritis and this untoward and often serious side effect soon led to its exclusion from clinical medicine. I mention this primarily to emphasize that minor alterations in the basic structural formula of a drug may be profoundly important in determining the character of the toxic reactions it produces.

Another interesting example of a toxic effect apparently due to the direct action of the therapeutic agent is the neurologic disturbance caused by stilbamidine. This drug, as you know, has been used in the treatment of trypanosomiasis, leishmaniasis, multiple myeloma, and systemic mycotic infections, especially blastomycosis. The administration of stilbamidine for a period of several weeks frequently results in anesthesia of the area innervated by the sensory division of the fifth cranial nerve. It is of interest to note that the same sort of regional anesthesia is produced by the inhalation of trichlorethylene. These two drugs would not at first seem to have much in common, but it so happens that stilbamidine is the only member of the diamidine group that contains an ethylene linkage, and it is generally conceded that the peculiar effect on the sensory division of the fifth nerve is the result of this chemical configuration which is in some way concerned with the neurotoxic effect.

Many therapeutic agents can cause direct toxic effects on the kidneys, and one example is bacitracin which, as you know, in ordinary therapeutic dosage often causes a mild degree of albuminuria. If larger doses of the drug are given or if the drug is continued for too long a period, albuminuria may become excessive, nitrogen retention occurs,

and a nephrotic syndrome may be produced. The same type of phenomenon, developing even more acutely, may be seen following the administration of any one of the polymyxins. These antibiotics likewise are capable of producing neurotoxic effects by their direct action, usually in the form of paresthesias involving the hands, tongue and the circumoral area. All of us are familiar, of course, with the direct toxic effect of streptomycin and dihydrostreptomycin on the eighth nerve, and I need not elaborate any more on that particular point.

Another very interesting toxic effect which results, probably from the direct action of the compound, is seen following the administration of hydralizine (Apresoline), a drug which is commonly and often rather unwisely used for the management of hypertensive vascular disease. It has been noted, especially in those patients who have been given large doses of Apresoline for relatively long periods of time, that a peculiar rheumatoid state characterized by fever and arthralgia makes its appearance. This rheumatoid state may develop ultimately into a clinical syndrome, which is indistinguishable from that seen in disseminated lupus erythematosus.

Most of the toxic reactions to therapeutic agents, however, are indirect and these are mainly due to sensitization on the part of the patient. An outstanding example is hypersensitivity to penicillin. Toxic reactions to penicillin may be of varying types. One of the commonest forms is a dermatitis, which is often mild but may be severe. In more severe reactions the eruption is sometimes urticarial, in other instances the lesions simulate those of erythema nodosum, and in very severe cases there may be an exfoliative dermatitis which can be serious or even fatal.

Another type of reaction to penicillin is a serum sickness-like disease which is characterized by urticaria and arthralgia, usually associated with fever, and often accompanied by leukocytosis with an eosinophilia.

We are all familiar with the fact that sensitization to penicillin may result in severe or even fatal anaphylactic reactions.

Fever as the sole toxic response to penicillin may also be observed. This usually develops in from six to ten days after initial administration of the drug, and it is generally believed that this lag period before the fever first becomes manifest represents the interval required for the formation of antibodies by the patient.

In connection with these various types of toxic reaction to penicillin, it is worth noting that skin tests are of relatively little value in determin-

ing whether a patient is or is not sensitive to the antibiotic. A definite history of sensitization, on the other hand, is important, although there are many instances where it is possible, if the drug is given cautiously, to administer penicillin to patients who give a history of sensitivity. In cases of this sort the drug must be administered with extreme caution at first, and injections should always be made in one of the extremities so that a tourniquet can be applied, if necessary.

Reactions to streptomycin, in addition to the neurotoxic phenomena already mentioned, occur relatively often, and generally consist either of fever, skin eruptions, or of a combination of the two.

Para-aminosalicylic acid also frequently causes side effects, chiefly consisting of fever and cutaneous eruptions. In certain instances a very peculiar picture simulating infectious mononucleosis has been seen following the administration of this drug.

It is fortunate in the case of isoniazid that toxic reactions are extremely rare. When they do occur they generally assume the form of a peripheral neuritis, and it has recently been reported that this toxic neuritis probably results from the fact that administration of isoniazid increases the excretion of pyridoxin. It has been shown that peripheral neuritis caused by isoniazid can be prevented by adequate doses of pyridoxin or vitamin B_6.

The tetracycline derivatives and chloramphenicol rarely produce allergic reactions, but such reactions have been reported and have mainly consisted of skin eruptions, either urticarial or eczematoid in type, or resembling erythema multiforme. In some instances fever has been described as well as a serum sickness-like illness. However, most of the so-called toxic effects of the broad-spectrum antibiotics can be related to their action on the bacterial flora of the gastrointestinal tract, and the changes in the bacteria which they induce are frequently followed by distressing symptoms in the patient. One of the common consequences is diarrhea in which it may be found that Monilia have largely replaced the normal bacterial flora of the bowel. In other instances the enterobacteria may be almost entirely supplanted by staphylococci, sometimes leading to a severe and at times even fatal enterocolitis. In addition, members of the genus Proteus and Pseudomonas often represent the replacement flora in the lower gastrointestinal tract of persons receiving broad-spectrum antibiotics, and secondary infections with these organisms are by no means uncommon.

In connection with the sulfonamides we may note in passing that they are not used so frequently as they were formerly, and that the drugs now currently employed are chiefly sulfadiazine and Gantrisin, which rarely produce toxic side effects. When side reactions occur they generally consist of a febrile disturbance, skin eruption, or a form of serum sickness-like disease.

Leaving the antibiotics and chemotherapeutic agents, I would like now to point out that the administration of chlorpromazine has been frequently reported to be associated with a peculiar type of hepatic disorder. Patients under treatment with chlorpromazine may develop jaundice, and liver function tests have indicated that the jaundice is of the obstructive type with elevation of the serum alkaline phosphatase, a rise in serum bilirubin mainly of the direct variety, and an increase in BSP (Bromsulphalein) retention. The cephalin flocculation reaction is usually negative and the thymol turbidity test gives variable results. Many patients with a toxic reaction to chlorpromazine of this type have been operated on for obstructive jaundice with the mistaken diagnosis of mechanical obstruction in the biliary system. A similar hepatic disorder has been noted previously in patients who have been given arsphenamines, methyltestosterone, and, in rare instances, thiouracil. It is believed that hypersensitivity is the responsible mechanism.

Lastly, I would like to make one brief reference to rauwolfia, merely to point out that in some instances this drug may cause sodium retention, and that its administration may lead to edema and congestive failure in patients with an established cardiac condition.

MODERATOR REZNIKOFF: Thank you, Dr. Rose.

We will next hear from Dr. Stern, who will talk to us about the psychiatric aspects of this subject.

DR. MARVIN STERN: For purposes of focusing the discussion a little more sharply, I would like to talk only about those major psychiatric reactions sometimes associated with the use of some drugs, namely, the psychotic reactions, and direct most of my attention to the so-called organic psychotic reactions which tend to fall into two main groups: acute psychoses, which go by various other designations familiar to you, namely, the acute toxic reaction, or acute delirium, or the so-called toxic infectious psychoses; and the chronic psychoses which are also produced by many of the same agents which produce the acute picture.

In considering the symptomatology of the acute psychotic reactions

there are certain aspects which might be highlighted. First, there is a clouding of the consciousness; there is an impaired awareness of what is going on around one; and the attention to the outside surroundings seems to vary a great deal; orientation for time, or person, or place is also irregularly and variously involved but always is involved in these acute psychotic reactions.

Secondly, they present visual and auditory hallucinations as fairly common concomitants of their psychoses.

The third factor which is quite significant is that these patients usually demonstrate marked emotional lability and as a general rule, tend to show marked anxiety.

The fourth factor is in terms of aberrant motor behavior. The motor behavior of these patients may show anything from gross tremors, such as characterize delirium tremens, to movements which are purposeful in dealing with their psychotic ideation.

In contrast to the rather florid picture as presented by the acute psychotic reactions, the chronic reactions are characterized by a much more serious memory impairment, usually greater for recent than for remote events, and by a general intellectual deterioration.

I think it is important to point out at this time that both sets of changes can be produced by a great variety of drugs and I would like to list them now and discuss them a little later when we present some of the problems and evaluate some causes of these changes.

In general, the first group might include the central nervous system depressants. As a group, the barbiturates and bromides are well known to produce psychotic reactions; the morphine group to a much lesser extent—and this I will discuss a little later. Dr. Rose has mentioned reserpine; and recently the literature has cited numerous examples of depression following its protracted use. This is not an organic psychosis but rather a functional reaction. In the group of central nervous system stimulants, amphetamine would be a good example. Autonomic drugs which are known to produce psychotic effects are atropine and scopolamine. The antimalarials also have been known to produce psychotic reactions, and these would include quinine and atabrine. The heavy metals, such as mercury and arsenic, carry their own characteristic picture. Because of their importance in producing psychotic reactions, the steroids deserve special mention.

I would like to point out that, insofar as the diagnosis of these psy-

chotic reactions is concerned, in terms of predicting what agent is responsible for the particular psychotic reaction, the psychiatric picture is far less of a guide to diagnosis than are the laboratory findings which usually make the differential diagnosis.

The first question which usually is raised in evaluating these various states is: Are these reaction types for different drugs distinguishable from the others? Before we go into that I should like to mention that ordinarily the psychotic picture is described under two major headings, namely, what is the form of the psychosis; and secondly, what is its content? By form of psychosis we ordinarily mean, "Is this the picture of an acute delirium, is this a stupor, or is this a wildly hallucinated individual, or one who retains his orientation?" etc. By content we mean what is produced as verbalizations by the patient during the course of this particular disturbed episode. I think it is important to point out that all of the investigators who work with these psychoses feel that the form and content run a course independent of the inciting agent so that these would not be particularly helpful in making a differential diagnosis.

What factors are involved which influence the reaction? First, is the intensity of biologic disturbance. Apparently those patients who are more seriously ill medically or surgically also tend to be more disturbed psychiatrically. Second, the environmental stimuli during the illness form a background for production of various kinds of content. I think this is extremely important. For example, in common usage if one describes a typical alcoholic delirium tremens, one would ordinarily anticipate that the patients would produce evidences of seeing little mice or little men or pink elephants running around the room. Yet, clinical experience teaches us that the quality of the hallucinations is much more in relationship to the life experience of the patient. Combat veterans in the South Pacific would hallucinate Japanese tanks as a very favorite kind of threatening object. In a city, trucks, trains and moving cars tend to form a background for the production of hallucinatory material. Also, because these people are extremely receptive to external stimuli, though they tend to distort them, what is in their immediate hospital setting becomes a focus for hallucinatory experiences. The specific equipment and life experience of the individual usually determine the character of the hallucinatory experience. So one would expect that a young person, an adolescent, in an hallucinatory experience would be preoccupied with the material which is characteristic of this age

group. Such a patient would be preoccupied with problems concerned with authority, and goodness, and sex, while patients in the older age groups would have a different kind of screen upon which they would project their fantasy and delusion.

Mentioning these things briefly, we can move on to the next set of factors, namely, what are the individual factors which determine the kinds of psychotic response? I think it is important to point out that not all individuals who are similarly exposed to known toxic agents show reactions. Also, when the organic reactions do occur in response to the same stimulus, they differ markedly in their characteristics. Some feel that the pre-psychotic personality may give a very good clue as to the kind of psychotic reaction which may appear later. For example, in working with the alcoholic group it has been noted that the pre-psychotic personality of the patient who develops what is called the Korsakoff psychosis is likely to be described as more "outgoing." He has the characteristic personality traits which accompany the telling of tall stories, which the introverted group does not commonly show. Patients who develop alcoholic hallucinosis have a different kind of personality makeup, usually described as schizoid.

Also, an interesting and significant fact is that patients may react in precisely the same kind of way to differing noxious agents. I have in mind a patient who developed a paranoid and confused episode following the administration of relatively small doses of ACTH for lupus erythematosus. She was cleared of the psychosis after the drug was withdrawn. Because of evidence that some drugs of the atabrine group may be beneficial in this disease, she was then started on atabrine. She responded with precisely the same kind of psychotic reactions in terms of content and form that she did with ACTH. This patient makes a good clinical point.

I think it is important to have some kind of neurophysiologic correlation. We can see that those agents which act directly upon the central nervous system may result in a different set of reactions than those which do not act directly.

We may also see another phenomenon—and this has been questioned by some—the so-called release phenomenon, and perhaps this might be illustrated in this way: A patient may be admitted to a hospital with a bromide psychosis. After the excretion of the excessive amounts of bromide, sufficient to return blood levels to normal, the patient may

continue to remain in a chronic psychotic state which is indistinguishable from schizophrenia. What is postulated is that these reactions represent a kind of release phenomenon, taking away inhibitory factors and permitting this other kind of reaction to be manifest when the cortical controls are not so strong. Most of what we see in these reactions is an indication of how completely brain function is disorganized, and the recovery rate is in relation to that portion of the brain which is not severely involved in the pathologic process.

I would like to mention some of the agents which are important in the treatment of neuropsychiatric disturbances and which produce psychotic reactions. For example, morphine, while producing many symptoms of both a psychological and physiological character, rarely produces psychotic reactions. When these psychotic reactions are produced they generally occur in individuals who are considered to have been prepsychotic or actually psychotic before morphine administration, or morphine addiction may have been present.

With the barbiturates the problem is quite different,—two types of psychotic responses are seen: First, in addiction to barbiturates or in large overdoses (often with suicidal intent) one can see the development not only of ataxia, dysarthria, and a clouding of the consciousness, but also the development of hallucinations and delusions. In the abrupt withdrawal of barbiturates, specific symptoms may also develop. However, it is important to note that these symptoms develop only under certain conditions. These are, first of all, that the patient must have been receiving a minimum of 1 to 2½ gm. of barbiturates daily for at least a month. Apparently, in doses less than this the withdrawal symptoms are not seen. Tremors and restlessness develop within eight hours after the last dose of barbiturate, and convulsive seizures are a frequent concomitant of this syndrome. As a matter of fact in one of the series reported from the U. S. Public Health Service Hospital at Lexington, Kentucky, convulsive seizures occurred in 80 per cent of the group from whom barbiturates were abruptly withdrawn. The psychotic picture is also frequently seen following abrupt withdrawal but in somewhat lower incidence than the convulsive seizures, and tends to appear somewhat later in the picture. It may appear usually within four to seven days after the barbiturate has been withdrawn, and tends to disappear spontaneously whether the patient is treated with more barbiturate or not. However, the course is considerably more stormy if barbiturate is not

resupplied to the patient.

The bromide psychosis has been discussed at length previously, and I would only add that in the absence of a positive history and without evidences of a high blood bromide level we are unable to differentiate it, except by minor clues not related to the psychiatric picture, from any other organic toxic psychosis.

I should like to close with brief mention of one group of drugs that have caused a considerable amount of discussion and for good reason, namely, the steroids. These preparations are used in the treatment of the collagen diseases as well as for a host of other diseases. I think it is important to point out what variables are involved and which seem to influence production of psychoses in those who are receiving these drugs. From the standpoint of classification the following psychotic reactions are seen: In our series, organic reactions with a delirium component tend to dominate the entire diagnostic panorama. They form more than half of all of the patients admitted to our hospital with steroid psychosis. We see in lesser percentage, a group of patients who also demonstrate clouding of consciousness, delusions and hallucinations but who also seem to become psychotic on smaller doses than the first group mentioned, and who seem to run a course which is not so directly related to concentration of the dose. These mixed schizophrenic and organic pictures tend to last longer than the two or three weeks that are characteristic of the typical organic psychosis. While giving these drugs, often given to patients who are seriously and critically ill, whose adjustment to life is threatened constantly (not only as it is in most cases by threat of death but also in some few by threat of recovery), we may witness the appearances of acute schizophrenic reactions. We may also see, in a fairly significant proportion, the development of pure mood disorders with pathologic euphoria or with severe depression associated with administration of these drugs. The dosages at which patients may present these reactions are much less predictable than those in the delirium group who develop the organic reactions. We can relate these reactions roughly to dosage, to the underlying disease and its complications, and also, I believe to a lesser extent, to the attitude of the physician. To demonstrate how the physician's enthusiasm may produce these euphoric reactions, I recall a young boy we were asked to see who had rheumatoid arthritis, of not too serious a character, for about five years. He was started on ACTH, by an enthusiastic physician, early in the

course of the experimentation with this medication. This enthusiastic attitude was picked up by the patient. After his first dose of 25 mg. of ACTH the ward staff were much disturbed to see him running down the ward doing hand springs and cart wheels exclaiming how good he felt. They were properly concerned and were also properly concerned with the rebound phenomenon which did occur after the withdrawal of the drug. He became unusually depressed and was then transferred to the psychiatric service for consultation and treatment. This demonstrates the influence of the physician's attitude about the medication as well as the unrealistic hopefulness of the patient, in relation to the resulting psychiatric picture.

I don't think I have to discuss the treatment of the psychoses but perhaps this can be developed during the question period.

MODERATOR REZNIKOFF: Thank you, Dr. Stern. I hope that some of the audience will ask questions about treatment. We have now discussed two phases of this subject. The interesting feature of Dr. Stern's remarks was that very often the emotional reactions of the patient to these drugs really are accentuations, if I understood him correctly, of a person's previous personality. You can't depend on that however. I remember a gentleman who was a perfect husband; used to come home every night, kiss his wife, give her his pay envelope once a week, help wash the dishes, etc. One night, he came home, she put out her lips for a kiss, he smacked her in the jaw and she landed at the other end of the room. The police smelled his breath, and couldn't find any alcohol. It was not until a physician came and took a careful history, that it was found that he was suffering from methyl bromidism. Maybe that was his personality, but he had kept it well in check.

The next speaker, Dr. Wasserman, will talk to us about the hematologic phases of this subject.

DR. LOUIS R. WASSERMAN: The rapid developments in therapy and ready availability of most therapeutic agents have brought about a marked increase in the toxic reactions affecting the hemopoietic system. It is not infrequent for dangerous, even fatal, complications to occur following the injudicious use of some of these agents. Thus these side reactions may constitute a more serious hazard to the patient than the disease for which treatment has been given.

The extent of the toxic reaction affecting the blood or bone marrow appears to bear little or no relationship to the dose administered; unusual

TABLE I

TOXIC RESPONSE OF HEMATOPOIETIC TISSUE TO THERAPEUTIC AGENTS

I. TYPE RESPONSE
- A. Hypoplastic or Aplastic Anemia
- B. Myelofibrosis
- C. Agranulocytosis
- D. Thrombocytopenia
- E. Hemolytic Anemia
- F. Leukemia?

II. MECHANISM
1. Direct Toxic Action
2. Hypersensitivity
3. Stimulation

side reactions to prior therapeutic trial enhance the probability of a toxic response to a subsequent course of the agent; and only if recognized early may the hypoplastic state be reversible.

Although only a small percentage of the population exposed to these therapeutic agents is affected adversely, nonetheless an appreciation of the possible side reactions and early recognition of them are essential if grave consequences are to be avoided.

Thé varieties of toxic responses of the hemopoietic system are noted in this slide (Table I). The first four groups have been classified by Osgood under the "Hypoplastic Syndromes" and, together with the drug-induced hemolytic anemia, represent the greatest number of the toxic responses of both the blood and bone marrow. The development of leukemia has been included as a possible result of toxic damage to the marrow because of the circumstantial relationship to benzol derivatives, radium and other radioactive isotopes and the increased incidence in radiologists. To this group one should also add the occurrence of lupus erythematosus cells in (1) hydralazine-treated individuals who manifest simultaneous serum disease symptoms; and (2) in severe allergic states due to penicillin. This L.E. phenomenon probably represents some disturbance in the enzyme systems of the white cells and plasma.

The most common mechanism for these toxic syndromes may be ascribed to the group of hypersensitive reactions. In those cases mani-

festing an explosive onset, within hours, of one of the hypoplastic syndromes, some type of antigen-antibody reaction involving one or more specific cell types in the peripheral blood must be postulated, and in many instances of hemolytic anemia, thrombocytopenia, and agranulocytosis due to drugs, such antibodies have been found. A hypersensitive mechanism has also been thought to act on the bone marrow hematic cells with a maturation arrest of the myeloid elements or megakaryocytes.

In these cases, the drug apparently acts as a haptene forming an antigenic complex with a specific cell protein leading to the formation of an abnormal antibody such as a hemagglutinin or leukagglutinin with a resultant hemolytic anemia or agranulocytosis. The presence of the drug may or may not be required for the action of the antibody on the red and white cells but in the case of platelets with thrombocytopenia the drugs appear to be necessary for the *in vivo* as well as the *in vitro* demonstration of the hypersensitivity reaction.

In those hypoplastic reactions of a more chronic nature which occur only after prolonged use of an agent such as x-ray, the mustards, the antifols and others, the direct toxic inactivation of one or more of the enzyme systems of the marrow cells may be important, but even in those cases occurring after chronic drug exposure such as chloramphenicol, the same hypersensitivity mechanism probably accounts for a large number of the hypoplastic states.

Time does not permit a listing of each and every agent implicated in these hypoplastic syndromes. It is important to understand that few if any of the drugs including antibiotics utilized by us at this time are devoid of occasional to rare toxic manifestations.

Whatever the mechanism for the production of hypoplastic states, whether by direct action on the enzyme systems of these primitive cells or by some hypersensitivity reaction involving a panantibody acting on these marrow elements, it must be due to either an inhibition of cell division or a block in the development of the cells. When primitive cells divide, one cell must remain immature to continue the process of cell division whereas the other divided cell matures and is destined for delivery into the circulation as an erythrocyte or granulocyte. A defect in any of the biological processes controlling this division and maturation of the hematic precursor cells may produce a hypoplastic state.

The findings in aplastic anemia, secondary to some toxic agent, are

similar to those of the idiopathic variety with pancytopenia and an empty marrow. Although it is possible that early in the course of the toxicity there may be a generalized maturation arrest, one is more prone to see hypocellularity with an increased fat content in the marrow. If fibrous tissue proliferation ensues, this usually occurs after a prolonged period of exposure and may actually be an end result of bone marrow aplasia.

A partial list of agents producing agranulocytosis may be seen in this slide. One should note that chlorpromazine has been implicated rather frequently of late in the production of granulocytopenia and that hydralazine will not only produce an agranulocytosis but simultaneously L.E. cells may be found if the slides are examined carefully.

Similar mechanisms, as mentioned previously, are involved in the production of agranulocytosis. In those cases secondary to drug toxicity the hypersensitive reaction appears to be the most common with circulating antibodies against granulocytes demonstrable in the blood in some cases. As in thrombocytopenia, however, there is good evidence that there is a dual action of the hypersensitive reaction. Thus, not only do the leukagglutinins act peripherally with agglutination or lysis of the granulocytes but a marrow effect with a maturation arrest is frequently seen.

The degree of leukopenia is not necessarily an index of the dosage of the drug administered and may range as low as a few hundred white cells.

The appearance of monocytes in the blood indicates recovery and may be taken as a good prognostic sign. This is seen on the left hand slide here. As has been stated before, two types of marrow reaction may occur, that showing hypoplasia of the myeloid elements due to inhibition of cell division, probably the most common marrow response, and that showing a maturation arrest at an early myeloid level. The type of marrow found may also be a function of the time at which the aspiration is performed. Following a period of inhibition of cell division there may be a proliferation of primitive white cells at an early cell level. A marrow showing such a maturation arrest is demonstrated on the right hand side of this slide with the block at the myelocyte level.

This case of agranulocytosis was due to one of the barbiturates with the course depicted in this slide (Fig. 1). The patient was admitted to the hospital for a neurologic complaint, given one capsule of the offend-

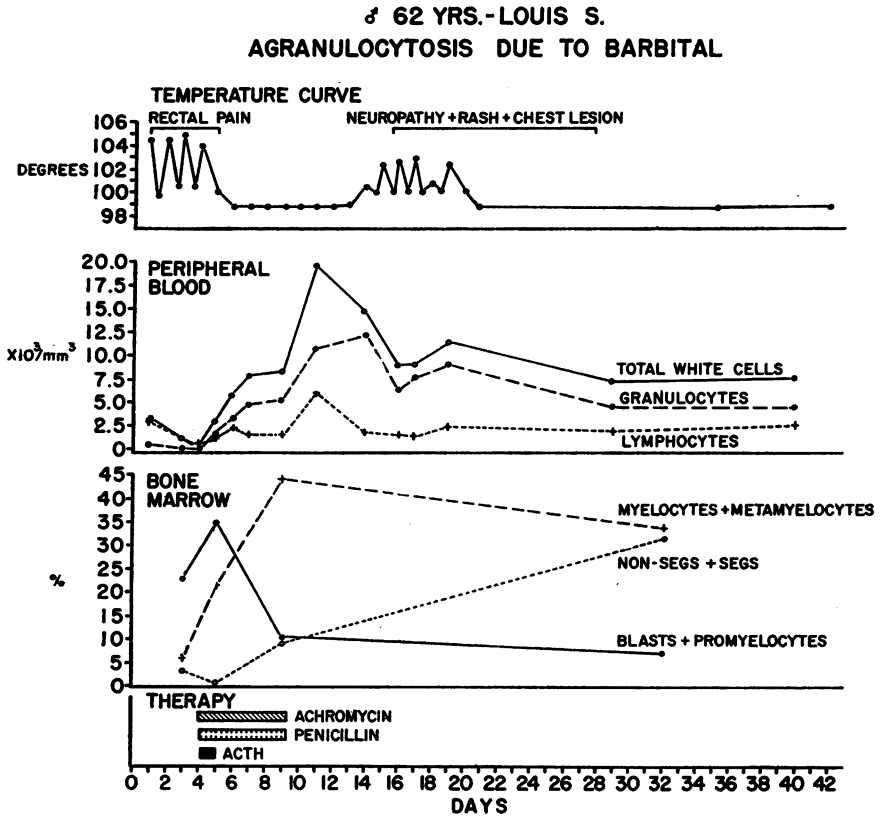

Fig. 1

ing agent for sleep the first night and developed the events shown here with a severe granulocytopenia. Following the leukopenic phase there is frequently a rebound with a leukocytosis as is demonstrated here. Recovery was complete in this patient.

Most of the agents causing thrombocytopenia are to be found in the lists already discussed. It would be difficult to exclude any drug from causing one or more of the hypoplastic syndromes.

The most common mechanism responsible for drug induced thrombocytopenia is again that of hypersensitivity. Ackroyd in studying the mechanism of Sedormid purpura demonstrated the development of platelet agglutinins and lysins which under special conditions could produce thrombocytopenia. These same antibodies presumably also act

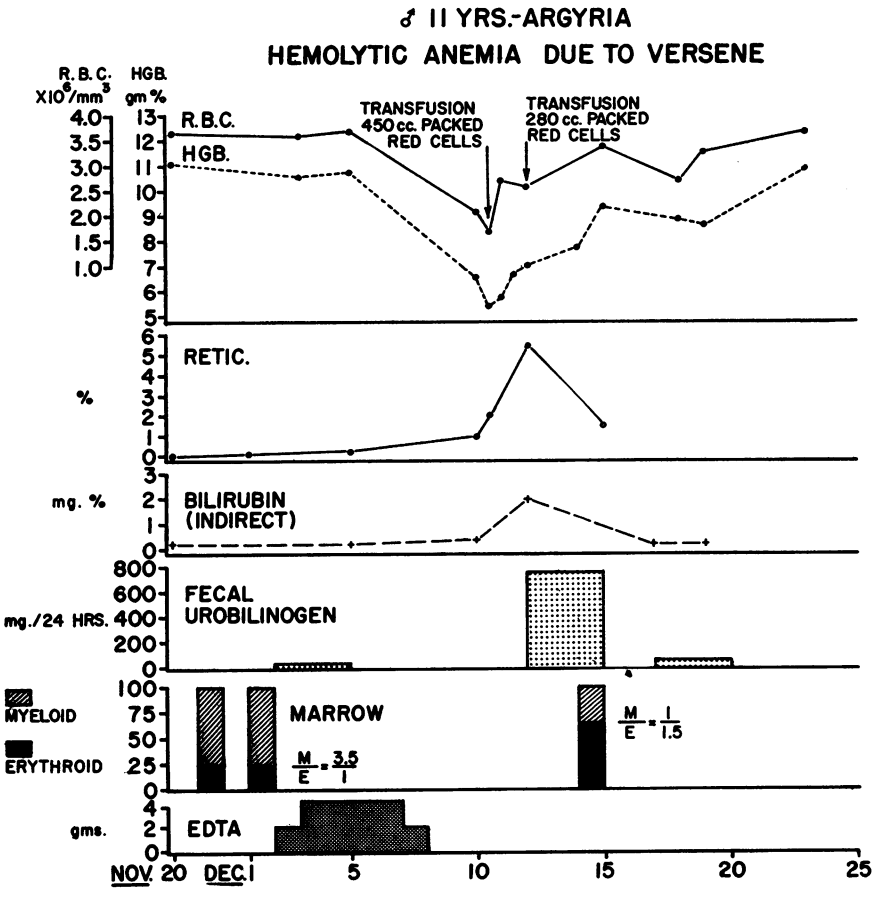

Fig. 2

on the megakaryocytes for one sees a maturation arrest of these platelet precursors as well. It is difficult to ascertain whether a third mechanism for thrombocytopenia, that due to R-E stimulation, is occasionally involved. The rapid disappearance from the peripheral blood of platelets or other cellular elements when antibodies cannot be demonstrated by our most delicate techniques would speak for an increased phagocytosis by the R-E cells of platelets, red cells or white cells presumably sensitized by opsonins or other immune bodies.

The usual blood findings associated with thrombocytopenia are seen in this slide. In the bone marrow one may find a diminution or even absence of megakaryocytes in those cases exposed to the anti-neoplastic

agents or drugs affecting the marrow directly. Where a hypersensitive mechanism exists one frequently finds a maturation arrest of the megakaryoblasts and perhaps an eosinophilia. Since this same picture may be found in thrombocytopenia not drug-induced, the differential diagnosis frequently must rest on a good history.

The characteristic purpuric rash seen in a case of thrombocytopenia, this due to quinidine, is seen in this slide. Although anti-platelet antibodies could not be demonstrated in the serum directly by the usual methods, inhibition of clot retraction by the Ackroyd technique was positive. The only tube containing patient's blood plus quinidine, tube #4, revealed no retraction of the clot with retraction in all the controls.

Hemolytic anemia may be caused by any one of a large number of drugs, a partial list of which is seen in this slide. Amongst the newer agents implicated are Versene, Aureomycin and Benadryl.

An example of Versene-induced hemolytic anemia is seen in this slide (Fig. 2). This 11 year old boy with marked argyria was treated with Versene when it first became available three or four years ago. Fortunately, hemoglobin pigment balance studies were being performed for other reasons, when there occurred a sharp drop in hemoglobin and red cells, a rise in bilirubin and reticulocytes, a change in the myeloid: erythroid ratio in the marrow and a tremendous increase in fecal urobilinogen excretion. With discontinuance of the medication the blood picture reverted to the pre-hemolytic state.

In the next slide are noted the various mechanisms involved in the causation of drug-induced hemolytic anemia. In this syndrome the direct action on the circulating red cells plays a most important role. Since the red cell life span is so long any central marrow effect would not be obvious for many days or weeks. Drugs causing hemolytic anemia produce changes in the stroma as well as the hemoglobin of the erythrocyte with Heinz bodies, fragmented red cells and the abnormal hemoglobins met- and sulf-hemoglobin.

The hypersensitive mechanism is probably again important even though immune antibodies may be difficult to demonstrate. The findings in the peripheral blood may be diagnostic of a drug-induced hemolytic process if Heinz bodies are searched for, and one notes fragmented cells or the peculiar brownish red cells of methemoglobin or sulfhemoglobin blood. The marrow shows an erythroid hyperplasia characteristic of all hemolytic processes.

TABLE II

THERAPY OF DRUG INDUCED BLOOD ABNORMALITIES

1. STOP THERAPEUTIC AGENT
2. FRESH BLOOD TRANSFUSIONS
   a) Collected in plastic bags or silicone-treated bottles
   b) Polycythemic blood
   c) Platelet transfusions
3. ANTIBIOTICS
   a) If platelets are low, avoid intramuscular injections
4. STEROIDS?

One final possible toxic reaction remains to be mentioned. We have been impressed for some time with the occurrence of acute blastic leukemias as an end stage of aplastic anemia induced by drugs, hair dyes, arsenobenzol derivatives and radiation. The cause and effect relationship of the last appears to be better documented than the former agents. Nevertheless it appears to be more than chance that three of our patients dying of blastic leukemia gave a history of long exposure to arsenic compounds. Certainly if cancer can be ascribed to arsenic it does not appear far fetched to suspect the chemical as an etiologic agent in acute leukemia. In two other patients dextro amphetamine had been taken for months preceding the onset of the leukemia. If radiation can induce a greater incidence of leukemia in those radiologists chronically exposed to it, radiometric agents may similarly produce abnormal cell proliferation. We postulate that the toxic agent acting on the bone marrow may produce areas of hypoplasia. The reparative stimuli are altered in some way, producing abnormal fibrous tissue and hematic cell proliferation and perhaps even leukemia. Speculation such as this does not appear to be too remote from the actual occurrences.

The therapy of these toxic manifestations of therapeutic agents is simple but not always successful (Table II). First and foremost the drug must be stopped. Transfusions, if necessary, should be with fresh blood and preferably collected in plastic bags or silicone treated bottles if viable platelets are necessary. We have not had too much success with platelet transfusions but it may well be that with better and easier methods of preparation these platelet transfusions will become more

useful. The introduction of antibiotics has certainly improved the prognosis in these hypoplastic states. Any of the broad-spectrum antibiotics can be used but if thrombopenia is present, injections are best avoided because of the danger of hemorrhage. The case for steroids still is obscure, but where a hemorrhagic tendency exists cortisone or Metacorten should be used.

Where a potent therapeutic agent must be used, an appreciation of the dangers which might occur would call for a careful blood count prior to therapy to be followed by frequent blood examinations as well as a careful appraisal of the physical status for hemorrhagic phenomena, sore throat, fever, arthralgias. Much has already been said and written about the use of potentially dangerous agents for treatment of minor disorders. Certainly the majority of toxic drug reactions would not have occurred if the risk of the disease had been weighed against the dangers of the drug used.

MODERATOR REZNIKOFF: Thank you, Dr. Wasserman.

I have a few questions, and all directed to Dr. Rose. The first one is this: How does the general practitioner determine whether Monilia infection is the cause of the patient's untoward symptoms of gastrointestinal disturbance, such as diarrhea, etc.?

DR. ROSE: He obtains a specimen for culture.

MODERATOR REZNIKOFF: *And that is the only way you can tell?*

DR. ROSE: As a matter of fact it can easily be determined merely by examining a stained smear of the feces.

MODERATOR REZNIKOFF: *I suppose if a practitioner is using an antibiotic, and he finds his patient is suddenly complaining of pruritus and diarrhea, he should be sufficiently alert to suspect that the drug may be causing the trouble?*

DR. ROSE: I should imagine so, and I think that most practitioners have the equipment to do a Gram's stain of the material obtained. Instead of finding predominantly gram-negative bacteria they would see large gram-positive organisms which could hardly be mistaken.

MODERATOR REZNIKOFF: *The next two questions are really the same. Can the gastroenterocolitis following the use of tetracyclines be ameliorated by the combined use of anti-fungal remedies (mycostatin)? And part of another question a good deal like it: Dr. Rose, does the addition of mycostatin to the antibiotic prevent the gastrointestinal disturbances that may follow the use of the antibiotics alone?*

DR. ROSE: I am sorry that I cannot answer the question. I have no information on the point.

MODERATOR REZNIKOFF: *Does anybody know? Dr. Wasserman!*

DR. WASSERMAN: No.

MODERATOR REZNIKOFF: *Dr. Stern!*

DR. STERN: No.

MODERATOR REZNIKOFF: My own experience is that we begin to use mycostatin after the apparent fungal infection arises, usually in the mouth. I have had no experience with its use in gastrointestinal conditions.

Does anybody in the audience wish to answer that question? (There was no response.)

Dr. Stern, I think this is directed to you: Kindly discuss in a little more detail the neurotoxic effects of streptomycin and dihydrostreptomycin.

DR. STERN: I think Dr. Rose mentioned it previously. Eighth nerve involvement is our chief concern. It is reported that the vestibular part of the eighth nerve is involved perhaps a little more frequently than the acoustic in dihydrostreptomycin therapy, while the hearing part is said to be more commonly involved in streptomycin therapy. I imagine that is the chief complication to be concerned with.

MODERATOR REZNIKOFF: *I shall ask Dr. Wasserman the next question: You include Phenergan among the antihistaminics capable of inducing agranulocytosis. Can you give us a reference in the literature offering evidence confirming such a claim?*

DR. WASSERMAN: Oh, yes. All these references were taken from well documented cases.

MODERATOR REZNIKOFF: I believe that is in a review by Osgood in 1953 in the *J.A.M.A.* and also in the *Annals of Internal Medicine*. Recently two articles, one by Vaughan and another by Stohlman in the *New York State Journal of Medicine* reviewed many of the drugs.

DR. WASSERMAN: This is from a list I received from a subcommittee of the American Medical Association listing all of the agents that had been implicated as causing hemopoietic disturbances. That drug was on the list.

MODERATOR REZNIKOFF: When I was in Argentina a few years ago doctors there told me that they never saw a case of aplastic anemia following chloramphenicol, and they used it constantly in large doses over

a long period of time for typhoid fever and other diseases. So you can see how people differ in their experiences.

Dr. Rose, a question was asked: Can digitalis produce a skin itch?

DR. ROSE: I am not familiar with it. It may occur.

MODERATOR REZNIKOFF: I would like to call your attention to the fact that patients are being given medications for some disorder, and it is sometimes a little difficult to determine whether the disease is not responsible for the toxic effect rather than the drug. However, I am not aware that digitalis commonly produces pruritus.

Another question: Is there any danger that Diamox may produce hepatic coma or disorientation in hepatic fibrosis of congestive failure? It goes on: These are reported in Laennec's cirrhosis after Diamox. How do mercurial diuretics compare in this respect? First of all we have a question whether Diamox may produce hepatic coma or disorientation in hepatic fibrosis. Are any of you gentlemen acquainted with that?

DR. ROSE: I am afraid my experience is not sufficiently extensive to permit me to answer the question, Dr. Reznikoff.

MODERATOR REZNIKOFF: One effect of Diamox that I know has been reported is acute neutropenia or agranulocytosis. I am not aware of any of these other conditions occurring.

DR. ROSE: I am not entirely certain in what context the question concerning mercurial diuretics is asked.

MODERATOR REZNIKOFF: *I think that the question is this: Here is a patient who apparently has cirrhosis of the liver probably secondary to congestive heart failure. I presume the patient has edema and either Diamox or the mercurials are used for the edema. Am I corrct? Is this the interpretation of the question?*

DOCTOR: That is right.

MODERATOR REZNIKOFF: *Then this gentleman wants to know if as a result of the use of Diamox or mercurial diuretics hepatic coma or some disorientation might occur?*

DR. ROSE: I certainly can answer the question with respect to mercurial diuretics. If these drugs provoke a good diuresis in an individual whose liver function is border line, so to speak, and if the patient is thereby over-dehydrated and the blood volume is reduced beyond a certain point, he may go into shock and ultimately display what is commonly called hepatic coma. I presume that if this can occur with the mercurial diuretics—and we know it does—that the same thing might

happen following Diamox, but what the comparison between the two drugs might be I do not know.

MODERATOR REZNIKOFF: In the old days when a patient had uremia and marked edema we used to treat him with hot packs, and we wondered why the patient had convulsions. Well, we assumed we got rid of the fluid but in accomplishing that, the toxic agents involved became more concentrated.

Are there any other questions from the floor?

If not, I should like to make a few statements by way of summary. This is a rather important subject not only to the patient but also to the doctor in several ways. Many doctors are being sued these days for accidents that occur, and they would like to know how they can prevent them. Unfortunately, we can't always prevent these accidents by sequential blood counts. We have all had the experience of having a patient who, early in the day has a normal blood count and that night develops acute agranulocytosis. Nor can we select our patients and determine who would be sensitive to what. There is no way of determining in advance who will respond in a bad way to a therapeutic agent. There are no animal experiments that can be used to determine what these agents will do. We know all patients will eventually show the depressing effects of urethane, Myleran, 6-mercaptopurine and radiation. We also know, however, that many patients will take many of these drugs that have been mentioned and shown on the screen without any untoward effect, and some will even have bad effects with a single or a few doses of aspirin. So the physician ought to use drugs when they are indicated and under no other conditions. He ought not to use drugs that might be toxic when he can use simple remedies; and after all is said and done he wants to be lucky!

I wish to thank the members of the Panel for their presentations and discussion and the audience for its interest and attention.